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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,994	07/02/2002	Frank Luyten		5817

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,994	LUYTEN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-61* is/are pending in the application.

4a) Of the above claim(s) *31-42 and 46-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-45,60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/3/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Preliminary Amendment, filed 4/3/02, has been entered.

Claims 31-61 are pending; claims 31-42 and 46-59 are withdrawn; claims 43-45, 60 and 61 are under current examination.

Election/Restrictions

Claims 31-42 and 46-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/4/05.

Applicant's election without traverse of Group XII (claims 43-45, 60 and 61) in the reply filed on 8/4/05 is acknowledged.

Information Disclosure Statement

Applicants' IDS, filed 4/3/02, has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-45, 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The invention is directed to precursor cells, which express a positive embryonic marker, which is either bone morphogenic or cartilage-derived morphogenic protein, a homolog thereof, or a marker co-expressed and/or co-detectable with the marker, and therapeutic compositions and implants comprising these cells.

Guidance of the Specification/The Existence of Working Examples. The specification teaches the isolation of skeletal precursor cells from human donors (Example 1), the *in vitro* expansion of these cells (Example 2), RT-PCR analysis of the cells, which indicated the expression of CDMP-1 (cartilage derived morphogenic protein-1) in only the skeletal precursor cell populations (Example 3), the skeletal precursor cells were then expanded (Example 4), and cultured in agaorse and injected intramuscularly into immunodeficient, nude mice (Example 5). The implant retrieved from these mice, 3 weeks post-injection, shows poorly differentiated fibrous tissue, reminiscent of periosteum (see pp. 26-27, bridging ¶). The skeletal precursor cells were induced to form cartilage *in vitro* by treatment of TGF-β1, 2, or 3 (Example 6). The specification teaches that the human skeletal precursor cells were intramuscularly co-injected with isolated pig articular chondrocytes into nude mice, and that 3 weeks-post implantation, the implants were analyzed and it was found that CDMP-1 is strongly down regulated as skeletal precursor cells enter chondrogenesis, and mature to the chondrocyte phenotype. Further, that the mature chrondrocyte is identified by the expression of various

markers, including BMP-2. The specification specifically teaches that CDMP-1 identifies the skeletal precursor cells of the instant invention.

State of the Art/Predictability of the Art. The specification provides a specific marker, CDMP-1, which is used to identify the cells of the claimed invention. The breadth of the claims are directed to identifying the claimed cells by expressed bone morphogenic proteins (BMPs) or CDMPs. The identification of cells by a particular marker is found to be unpredictable when the marker is expressed in various cell types, as one of skill in the art could not simply identify a particular and specific population of cells in this manner. For example, BMPs are a large family of proteins that belong to the TGF-β superfamily. Chang *et al.* (**JBC**, 45(11): 28227-28234 (1994)) state the following, "BMPs may have wide-ranging extraskeletal roles in development, as suggested by the following observations. 1) Localization studies in both human and mouse tissues have demonstrated high levels of mRNA expression and protein synthesis for various BMPs in kidney, lung, small intestine, heart, limb bud, and teeth. Several members of the family, including BMP-4 and =7 are key molecules in epithelia-mesenchyma interactions, for example during odentogenesis. BMP-2 and –4 are involved in the signaling pathway that controls patterning in the developing chick limb, and BMP-4 is a ventralizing factor in early *Xenopus* development." See p. 28227, 2nd column, first full ¶. Chang further state that, with regard to CDMPs, CDMP-1 is expressed predominantly in the precartilagnious mesenchymal condensation and throughout the cartilaginous cores of the developing long bones, whereas CDMP-2 expression is restricted to the hypertrophic chondrocytes of ossifying axial skeleton during human embryonic development. See Abstract. The instant specification provides the isolation of cells that express CDMP-1, and the expansion of these cells. The resultant cells were capable of forming cartilage *in vitro* upon treatment of TGF-β, but there is no specific guidance as to specific characteristics of the isolated cells, other than the expression of CDMP-1. The state of the art clearly shows that the breadth of the

claims is non-enabling, because the expression of a BMP or CDMP is not sufficient to uniquely identify a particular cell population; therefore, given the unknown nature of the resultant cells described by the specification, the cells lack an enabled use, as one of skill would not know how to use these cells in any of the contemplated methods. The claims are further directed to identification of the cells by a homolog, or markers co-expressed and/or co-detectable with a BMP or CDMP, and specific embodiments, a TGF-b having at least 80% homology with CDMP-1, or a marker or factor co-expressed or co-detectable with said positive markers, and further, that the cells are characterized by the absence of a negative marker, being FGFR3, or a marker or factor co-expressed with FGFR3 (claim 61). However, there is no specific guidance with regard to these specific markers, which could be identified as uniquely expressed by the claimed skeletal precursor cells, such that one of skill in the art could make and use these cells. For example, the specification fails to provide specific guidance with regard to isolation of cells using any of the markers, other than CDMP-1, in order to arrive at the claimed invention. There is no teaching or guidance with regard to markers or factors that are co-expressed with any of the contemplated markers that would allow the skilled artisan to uniquely identify the cells that are instantly claimed.

The intended use of the claimed implants or therapeutic compositions comprising the skeletal precursor cells is directed to implantation for the purposes of therapy. However, the state of the art of using stem cells for transplantation purposes is found to be unpredictable. For example, Hui *et al.* (**Ann. Acad. Med. Singapore**, 34: 206-212 (2005)) is post-filing art that supports that using stem cells, such as pluripotent mesenchymal stem cells, for therapeutic purposes, remains unpredictable, and if successful, requires specific conditions, considerations and method steps. Mesenchymal stem cells (MSCs), which can form various tissues, such as osteoblasts and chondrocytes, have been analyzed for musculoskeletal tissue engineering. Hui teach that the repair of, for example bone, require an

effective delivery scaffold, which has not yet been realized (see p. 208, 2nd column, 2nd full paragraph). Particularly, scaffolds which contain MSCs would need to maximize nutrient diffusion, interstitial fluid to control cell growth and function, and optimize scaffold mechanical function within the regenerated tissue (see p. 210, 1st column, 1st full ¶). Hui review the potential uses of MSCs in repairing various tissues, including tendon repair, but state that the regeneration of tendon tissue is limited, and there is a fundamental lack of knowledge of tissue-specific differentiation factors for tendons. See p. 211, col. 1, first ¶. Hui conclude by stating that, although MSCs may be well suited for tissue repair, "Future research should be directed better directed at a cell population, including identifying unique markers and mapping lineage development." See p. 211. Although the instant specification provides a single marker to identify the skeletal precursor cells, there is no guidance with regard to the intended use of the implants or therapeutic compositions comprising these cells for use in transplantation therapies. The working examples fail to correlate to a therapeutic result in utilizing the claimed cells, as they are directed to injection of immunodeficient, nude mice, which would not be considered a model for an immunocompetent individual. For example, it is well-known in the art that, upon injection of cells that are not autologous to the individual, the could fail to integrate into the host tissue, and function in an appropriate fashion. There is no support provided by the instant specification with regard to the injection/implantation of the claimed cells into an appropriate host, to enable the intended use of the claimed cells.

The Amount of Experimentation Necessary. The instant specification fails to provide teaching or guidance for the claimed embodiments of isolated skeletal precursor cells, because the methods taught by the specification only provide a particular marker , CDMP-1, to identify these cells. However, beyond using this single marker, the specification provides no other defining characteristics of the resultant cells. Although the working examples provide guidance with regard to the

production of cartilage from the cells, upon administration of TGF-β, this fails to provide guidance with regard to the actual cells that are isolated. The art shows that BMPs and CDMPs are expressed in a variety of cell types, some of which are more or less-lineage restricted. Furthermore, as noted by the instant specification, chondrogenesis and osteogenesis is a complex process that has a range of cell types (see Figure 1). Thus, given the teachings of the art, with regard to the expression of CDMPs or BMPs in order to identify a cell population, it would require undue experimentation for one of skill in the art to identify the particular cell population, as claimed, for any of the contemplated uses in the specification.

In view of the lack of teachings or guidance, with specific regard to the identification of the skeletal precursor stem cells, except by the identification of a particular marker (CDMP-1), the unpredictability in the art with regard to the intended use of the therapeutic compositions/implants for therapeutic purposes, the lack of teachings or guidance with regard to define the cells used in the working examples, the lack of nexus between the *in vivo* example, utilizing a nude, immunodeficient mouse and any resultant therapeutic effect, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Written Description

Claims 43-45, 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now*

claimed." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification provides no written description for the claimed invention (cultures of isolated and expanded viable, differentiated pluripotent precursor stem cells which express a positive embryonic marker, which is either bone morphogenic or cartilage-derived morphogenic protein, a homolog thereof, or a marker co-expressed and/or co-detectable with the marker, and therapeutic compositions and implants comprising these cells, and in specific embodiments, a TGF-β having at least 80% homology with CDMP-1, or a marker or factor co-expressed or co-detectable with said positive markers CDMP-1 (claim 60), and further characterizing the cells by the absence of a negative marker, being FGFR3, or a marker or factor co-expressed with FGFR3 (claim 61)) because the specification fails to describe what markers and the resultant cells would belong to this genus. Although the specification teaches that the cells of the instant invention are characterized in that they express CDMP-1, there is specific characterization of the cells to indicate that they are differentiated pluripotent precursor cells that have entered the post-natal skeletal differentiation pathway. The art recognizes that bone morphogenic proteins and CDMP are proteins that belong to the TGF-β superfamily (see above). Therefore, any protein in this superfamily would be considered a homolog of a BMP or CDMP. The specification does not describe what particular markers, homologs, or markers that are co-expressed or co-detectable with any marker, or markers with 80% homology with CDMP-1, or markers/factors that are co-expressed with FGFR3, that would be used in order to identify the cell population as instantly claimed, with any particularly, to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification, and which are not conventional in the

art **as of Applicants' effective filing date**. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient, relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in that art would recognize that the inventor had possession of the claimed invention. In the instant case, the claimed cells lack a written description, as the specification fails to describe what marker(s) would be specifically expressed in order to identify the claimed cells from a variety of other cells, which express markers encompassed by the instant claims. The skilled artisan could not envision which of the markers, encompassed by the claims, would be expressed in the cell population instantly claimed, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention, and reference to a potential method of isolating it.See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43-45, 60 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of the claims cannot be ascertained for the following reasons: claim 43 recites a "differentiated, pluripotent precursor cell". It is unclear how a cell can be differentiated and pluripotent simultaneously, as a differentiated cell is one that is highly specialized (see pp. 13-14, of the specification). A pluripotent cell can give rise to a differentiated cell, but it is unclear how the pluripotent cell is also a differentiated cell. Claim 43 recites "a marker co-expressed and/or co-detected with this marker" (see last line of the claim). This is unclear because it encompasses markers that are co-expressed but potentially not detectable with a particular marker. Claims 44, 45, 60 and 61 recite the same terms similarly, and are also found to be indefinite for the reasons cited above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43-45, and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Connolly (WO 98/35022, published August 13, 1998, cited on Applicants' IDS, filed 4/3/02).

The claims are interpreted as such: the claims require the expression of a BMP, CDMP, a homolog thereof, or a marker-coexpressed and/or co-detectable in a cell population. Thus, a population of cells need only require an expression of any of the above-mentioned markers in order to anticipate the claimed invention.

Connolly teach methods of identifying human mesenchymal stem cells using the expression of p21 cyclin inhibitor protein ($p21^{CIP1}$) (see Abstract). Particularly, they teach that $p21^{CIP1}$ is found to be implicated as an effector of the TGFβ signaling pathway (see p. 3, 1st paragraph). They further teach that the isolated cells can be used in methods for producing pharmaceuticals, and for methods of tissue repair, and further as *in vivo* implants for transplantation. See p. 4. Accordingly, because Connolly teach the isolation of cells that express a marker encompassed by the claims, they anticipate the claimed invention. Further, because the cells express a particular marker encompassed by the claims, they would inherently be cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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